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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUANG, EVELYN MEI	
ART UNIT	**PAPER NUMBER**
1625	10

DATE MAILED: 10/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/069,663	Applicant(s) ABERG ET AL.	
	Examiner Evelyn Huang	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-15 and 18-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-15 and 18-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-3, 6-15, 18-20 are pending. Claims 4, 5, 16, 17 have been canceled according to the amendment filed on 7-25-2003.

Specification

2. Applicant has submitted an abstract on the same page with the amended claims. An abstract ***on a separate sheet*** (not the first page of the PCT application) is required.

Claim Rejections - 35 USC § 102

3. The rejection for claims 1-3, 7-13, 19 under 35 U.S.C. 102(b) as being anticipated by Polivka I (CS 263993) or Polivka II (Coll. Czech. Chem. Commun. 1989, 54(9), 2443-69, PTO-1449) is maintained for reasons of record. The rejection is applicable to claims 14, 18.

Polivka's method of using the (-) ketotifen as an antihistamine is encompassed by the instant claim 7 (Polivka I, page 6, last paragraph). The avoidance of sedative side effect recited in the instant is inherent in the compound.

Racemate and pure enantiomers of ketotifen and their biological activities are described (Polivka I, pages 7-10, Examples 1, 3, page 6, last paragraph, page 7, second paragraph; Polivaka II, page 2456-7). The racemate and pure enantiomers of ketotifen anticipate the corresponding norketotifen racemate and enantiomers, since the administration of an enantiomer or racemate of ketotifen to an animal in need thereof would inherently lead to the corresponding norketotifen, which is a known metabolite of ketotifen (Le Bigot, Life Sciences, 40, 883-890, PTO-1449, page 889, Fig. 2; Drug Metabolism an Disposition, 11(6), 585-589, PTO-1449, page 586, Fig. 1). The instant method of using the racemate or optical isomers of norketotifen is therefore anticipated by the prior art method of using the racemate or optical isomers of ketotifen as an antihistamine. The lack of side effects of as recited in the instant is intrinsic to the compound.

Without providing evidence, Applicant argues that the skilled artisan has no reasonable expectation that the administration of the enantiomer of ketotifen would result in the same enantiomeric metabolite. Furthermore, racemization may occur.

Since it is well known in the biochemical art that enzymes in the biological system is chiral, and only one enantiomer would fit into the chiral active site of an enzyme, it is reasonable to expect the metabolite to be of the same configuration unless proven otherwise. Even if racemization does occur as suggested by applicant, the racemate is still made up of stereochemically isomeric forms of the norketotifen, and would fully meet the requirement of the instant claims wherein the degree of enantiomeric purity has not been recited.

Furthermore, inherent anticipation does not require that person of ordinary skill in art at relevant time would have recognized inherent disclosure. Claimed invention may be inherently anticipated even if prior art supplies no express description of any part of claimed subject matter, since prior art reference that expressly or inherently contains each and every limitation of claimed subject matter anticipates. Schering Corp. v. Geneva Pharmaceuticals Inc., 67 USPQ2d 1664.

The 102(b) rejection cannot be overcome by the Declaration, which has been fully considered by the examiner.

Claim Rejections - 35 USC § 103

4. The 103(a) rejection over Polivka I (CS 263993) or Polivka II (Coll. Czech. Chem. Commun. 1989, 54(9), 2443-69, PTO-1449) in view of Le Bigot (Life Sciences, 40, 883-890, PTO-1449) and Bourquin (3862156, PTO-1449) and Kofler (Experimental Chemistry. Organic Chemistry and Reaction. Pages 504-505, PTO-1449) is withdrawn for claims 1-3 in view of the amendment and the Declaration upon reconsideration, but maintained for claims 6-15, 18-20.

Pure enantiomers of ketotifen and their biological activities are described in Polivka I (pages 7-10, Examples 1, 3) and in Polivka II (page 2456-7). Alternative procedure for the resolution of the recemate is described by Kofler (pages 504-505).

While Poliveka I or II does not specifically discloses the enantiomers of norketotifen, as recited in the instant claims, administration of a pure enantiomer of ketotifen to an animal would

lead to the corresponding norketotifen, since they are known metabolites in vivo (Le Bigot, Life Sciences, 40, 883-890, PTO-1449, page 889, Fig. 2). The chemical synthesis of the 10-hydroxy ketotifen is also described by Bourquin (columns 5-6, Example 3).

While the above references do not recite the topical, dermal, transdermal, rectal etc. administration or different physical forms of the composition as recited in the instant claims 13-15, 18-20, such formulations and modes of administration are well known in the pharmaceutical art and are routines for one of ordinary skill in the art. The addition of another active ingredient of the same use, such as another antihistamine, in the composition comprising the antihistaminic norketotifen or (-) ketotifen for a more effective formulation is prima facie obvious to one of ordinary skill in the art.

Claim Rejections - 35 USC § 112(2)

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. For the method claim, the amount of the composition administered is missing but is required.

b. The claim only recites 'a method comprising administering to a mammal in need thereof a composition...'. The claim is indefinite since it is unclear what the mammal is in need of.

Claim Rejections - 35 USC § 112(1)

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-15, 18-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the inventive compounds to treat the diseases as recited in the specification, does not reasonably provide enablement for using the compounds for preventing or treating all the diseases as recited in the claims or for the method of administering to a mammal in need thereof a composition as recited in claim 20. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant method is directed to using the histamine H1 receptor binding compound for preventing or treating a respiratory disorder, allergic disorder, a dermal disorder, a gastrointestinal disorder or an ocular disorder. However, each of these is a class disorders encompassing diseases of diverse origins. For example, according to the Merck Manual (11^{th} Edition), the following diseases or disorders are described in Section 18, Respiratory (page 1266): pneumonia, pulmonary emphysema, atelectasis, tuberculosis, neoplasms, hypoxia....etc., each has different origins and requiring different treatments. One of ordinary skill in the art would have no basis to expect an H1 ligand to be effective in preventing or treating all these different respiratory diseases.

While some of the respiratory disorders, such as bronchitis, cough, COPD is treatable with an antihistamine, the prevention of these disorders is not possible since the criteria for determining the individuals who would develop these disorders have not been established.

Claim 20 is directed to a method comprising administering to a mammal in need thereof a composition, which comprises the norketotifen or S-ketotifen and one or more drugs selected from a laundry lists of different classes of active ingredients. Since it is unclear what the composition is for (see paragraph 5 above), one of ordinary skill in the art would not be able to make and use the composition as claimed without undue experimentation.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3, 6-15, 18-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Aberg I (WO 98/56381) or Aberg II (WO 98/43640, PTO-1449).

Aberg I (page 2) or II (page 6) discloses norketotifen, which can only be in the form of racemate or stereochemical isomers. The norketotifen in Aberg I or II therefore anticipates the stereochemical isomers as recited in the compound claims 1-3.

The method of using norketotifen for treating an ocular disease with less local irritation and less sedative effects than ketotifen (Aberg I, page 2, last paragraph; page 11, Claims 1-7) and the method of using norketotifen as an antihistamine or an anti-inflammatory agent without sedative effect (Aberg II, page 6, 1.; page 7, 3.) are encompassed by the instant claims.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7, 9, 10, 12, 13-15, 18-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6207684 (the US equivalent to WO 98/56381). Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented method of using norketotifen for treating an ocular disease with less local irritation and less sedative effects than ketotifen (column 1, lines 57-62; Claims 1-7) is encompassed by the instant claims.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 703-305-7247. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Alan Rotman can be reached on 703-308-4698. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Evelyn Huang
Primary Examiner
Art Unit 1625

October 18, 2003